Brief Reports

Immunoblastic lymphadenopathy: report of four new cases and review of the disease

B. BERRIS, MD, FRCP[C], FACP
B. FERNANDES, MD, FRCP[C]
I. ROTHER, MD, FRCP[C]

Immunoblastic lymphadenopathy was discovered when previously undescribed changes noted in the pathological examination of lymph nodes from 15 patients were correlated with clinical findings in the patients' records; Frizerra and associates[1] reported the newly recognized disease in 1974 under the name angioimmunoblastic lymphadenopathy with dysproteinemia. The following year Lukes and Tindle[2] reported similar findings in 32 patients and adopted the name immunoblastic lymphadenopathy. It soon became apparent that the two groups had described the same disease.

The clinical diagnosis of immunoblastic lymphadenopathy is important because this disease often responds well to steroids, but the disease is also of scientific interest because it has features of both an immunologic and a neoplastic disorder. To date 400 cases have been reported.[3] In this paper we present four additional cases (Table I) and review the disease.

Pathogenesis

The cause of immunoblastic lymphadenopathy is not known, but the laboratory and histopathological features suggest that it is an immunologic disorder. Drugs are often considered to be the antigenic stimulus, but it may be an autoimmune condition.[2-4] It shares many features with graft-v.-host disease[1] and appears to lie somewhere between benign "reactive" hyperplasia and immunoblastic sarcoma.[2] Unregulated proliferation of B (bone-marrow-derived)-lymphocytes in this disease may be due to impairment of the regulatory and suppressive functions of the T (thymus-derived)-lymphocytes.[5]

From the departments of medicine and pathology, Mount Sinai Hospital, Toronto, and the University of Toronto

Reprint requests to: Dr. B. Berris, Mount Sinai Hospital, Ste. 429, 600 University Ave., Toronto, Ont. M5G 1X5

Clinical features

Immunoblastic lymphadenopathy most commonly affects the elderly, and 90% of patients are over 40 years of age. There is no sex preference. Constitutional symptoms, such as fever, fatigue and weight loss, are found in about 75% of patients, and pruritus is common. There is often a history of previous drug ingestion.

Lymphadenopathy is almost invariably present, and hepatosplenomegaly is detected in approximately 65% of patients. A rash is common.[6] Neurologic,[7] pulmonary[8] and joint problems[9] are rare.

All four of our patients had constitutional symptoms, one had severe pruritus and one had polyarthritis. In one lymphadenopathy was minimal, and only two had hepatosplenomegaly. One had a history of drug therapy.

Laboratory features

Anemia occurs in about 75% of patients, and the Coombs' test has a positive result in about 50%. Leukocytosis or leukopenia, thrombocytopenia and eosinophilia are seen in about 35% of patients.[3,10] In some patients progressive pancytopenia occurs.[11,12] Hypergammaglobulinemia is very common, occurring in 77% of cases; it is more common for the IgM than the IgA serum level to be increased,[3] and occasionally monoclonal gammopathy is seen. Smooth muscle, anti-DNA or antimitochondrial antibodies and rheumatoid or antinuclear factor may be found in the serum.[10]

All our patients were anemic, but in none did the Coombs' test have a positive result. All four had an increased erythrocyte sedimentation rate. Two had leukopenia (in one it was severe), two had eosinophilia and three had thrombocytopenia. Hyperglobulinemia was present in all four patients; three showed an increased level of IgA alone, but the fourth showed an increased level of IgG as well. The latex fixation test gave a positive result in two, and the antinuclear factor test gave a strongly positive result in one.

Radiologic findings

Hilar and mediastinal adenopathy is fairly common and was seen in the chest roentgenogram of one of our patients. Other radiologic findings may include evidence of pulmonary infiltration or pleural effusion. Abdominal lymphangiograms may be abnormal.[3]

Pathological features

The features of immunoblastic lymphadenopathy demonstrated by biopsy have been established.[1,2,13] The cardinal ones are obliteration of normal architecture, a pleomorphic population of immunoblasts, lymphocytes and plasma cells, small vessel proliferation and interstitial eosinophilic deposits. However, the features may vary greatly within the same node and between different nodes,[2,13] as illustrated by our cases. In case 1 the first biopsy showed marked noncaseating, epithelioid granuloma formation (Fig. 1). This feature has been noted by others[2] and may lead to a mistaken diagnosis of infectious or other granulomatous disease of the lymph nodes.[14] Several reactive germinal centres were seen. The next biopsy specimen, which was diagnostic of immunoblastic lymphadenopathy, demonstrated a marked reduction in the size of the germinal centres. In cases 2 and 4 germinal centres were absent from the biopsy specimens, which were diagnostic. Fibrosis was prominent in the specimen from patient 2 and notable in that from patient 3 (Fig. 2); both had a good initial response to therapy and prolonged survival. In all cases the most numerous cells in the biopsy specimens were plasma cells. Immunoperoxidase staining for intracytoplasmic immunoglobulin demonstrated both κ and λ light chains,

indicating polyclonal proliferation. IgG-bearing cells were predominant, and there were minor populations of IgA- and IgM-bearing cells. This pattern was noted even in the patients whose serum levels of IgA were increased.

Severe hepatitis was detected at autopsy in patient 1. While this abnormality may be an integral part of the disease, the possibility of its being due to a toxic or infectious agent acting on a host with an abnormal defence mechanism cannot be excluded.

Course

Although its microscopic features appear benign, immunoblastic lymphadenopathy usually has a very serious prognosis: about half the patients die within 1 year and two thirds within 2 years.[10] Remission and exacerbations are common. Transformation to immunoblastic sarcoma may occur,[2] and it has been suggested that immunoblastic sar-

Table I—Clinical and laboratory data* and results of treatment in four cases of immunoblastic lymphadenopathy (IL)

Variable	Case no. 1	2	3	4
Patient's age (yr)/sex	61/M	46/F	74/M	90/F
Presenting symptoms	Pruritus, weight loss and fever for 2 months	Polyarthralgia, fatigue and weight loss for 1 month	Fever, fatigue and night sweats for 3 months	Intermittent fever and weight loss for 9 months
Antecedents	Myocardial infarction 3 months before	Meigs' syndrome due to struma ovarii (removed) 2 months before	Rheumatoid arthritis treated with ibuprofen and indomethacin for 6 months	None
Physical findings	Fever, lymphadenopathy, and hepatosplenomegaly	Fever, marked generalized lymphadenopathy and knee effusions	Fever, hepatosplenomegaly and minimal lymphadenopathy	Fever and lymphadenopathy
Hemoglobin level (g/dl)	11.7	11.3	12.1	9.1
Leukocytes				
Total count ($\times 10^9$/l)	2.4	6.1	9.0	11.4
% eosinophils	22	31	N	N
Platelet count ($\times 10^9$/l)	N	48	88	85
Erythrocyte sedimentation rate (mm/h)	50	77	38	70
Results of tests				
Liver function	N	N	γ-glutamyl transpeptide level 55 IU/l	N
Latex fixation	N	1:640	1:160	1:40
Antinuclear factor	N	1:320 (homogeneous pattern)	N	N
Immunoelectrophoresis	↑IgA	↑IgA	↑IgA and IgG	↑IgA
Coombs'	N	N	N	N
Diagnosis from lymph node biopsy	First: reactive hyperplasia with granuloma formation. Second, 6 months later: IL	IL	IL	IL
Treatment	Prednisone till death	Prednisone for 2 years	Prednisone for 2 years	Prednisone till death
Result	Remission for 9 months, then acute hepatic and renal failure, with death in 2 days	Remission for 19 months. Died of bronchogenic carcinoma	Remission for 16 months, but serum level of IgA still increased	Remission for 1 month, then sudden death of unknown cause
Total duration of illness (mo)	16	43	40	10
Autopsy findings	IL plus hepatic and renal tubular cell necrosis	Bronchogenic carcinoma; no evidence of IL		Autopsy not done

*N = normal or negative.

coma can coexist with immunoblastic lymphadenopathy, the features of the two disorders appearing in different areas of the same lymph nodes or in lymph nodes from different sites.[15] Patients without evidence of immunoblastic sarcoma live longer and respond better to therapy than patients with immunoblastic sarcoma.

Factors contributing to death in patients with immunoblastic lymphadenopathy are resistance to treatment, infection and the development of immunoblastic sarcoma, which occurs in up to 20% of patients.[13] Less commonly hemorrhage, acute renal failure or hepatic necrosis develops.

Three of our four patients died, two within 2 years after the onset of illness; one of the two (patient 1) died of acute hepatic and renal failure, but in the other (patient 4) the cause of death was unknown. Patient 2 died of bronchogenic carcinoma 43 months after she had become ill; the immunoblastic lymphadenopathy had been in remission for 19 months, and at autopsy no evidence of this disease was found. One patient was alive and well 40 months after diagnosis, his disease having been in remission for 16 months.

Diagnosis

Immunoblastic lymphadenopathy should be considered in the differential diagnosis of any systemic disease, particularly if lymphadenopathy is present. In a patient with fever, lymphadenopathy and a rash who is receiving drugs it may be hard to distinguish between a drug reaction and immunoblastic lymphadenopathy. If the lymphadenopathy involves the mediastinal and hilar nodes (as in case 2) the disease may mimic sarcoidosis; however, the patient with immunoblastic lymphadenopathy usually appears more ill and has a higher fever. Perhaps the most difficult clinical differentiation is between immunoblastic lymphadenopathy and Hodgkin's disease or lymphoma. As in our cases, the hyperglobulinemia plus other positive results of immunologic tests should suggest immunoblastic lymphadenopathy. When the immunologic tests give results compatible with a diagnosis of systemic lupus erythematosus (as in case 2) the presence of lymphadenopathy more prominent than is usually seen in this disease should make immunoblastic lymphadenopathy a serious consideration. Gamma heavy-chain disease may have a similar clinical presentation, but serum protein immunoelectrophoresis will suggest the correct diagnosis.[3] A definitive diagnosis, however, can only be made by lymph node biopsy. If the initial biopsy does not yield a diagnosis a biopsy at another site or sequential biopsies (as in case 1) may be helpful.

In our four patients the diagnosis was suggested by the combination of constitutional symptoms, lymphadenopathy and the increased serum levels of immunoglobulins and was confirmed by lymph node biopsy.

Treatment

Spontaneous remission is rare in immunoblastic lymphadenopathy. Prednisone and chemotherapeutic agents, alone or in combination, have resulted in remission, but no controlled studies comparing the efficacy of various therapeutic regimens have as yet been done. From our experience and evidence in the literature the use of prednisone alone as initial therapy seems logical.[16] All four of our patients had an excellent initial response to this agent, though two died while receiving it. Since the most serious complication resulting in death in such patients is systemic infection, and since the use of chemotherapeutic agents in addition to steroids would increase the risk of infection, combination therapy at the outset is not recommended. If a remission is not obtained with steroids alone, a chemotherapeutic agent, such as cyclophosphamide, might be added to the regimen. In patients with progressive pancytopenia[8,9] (such as patient 2) the use of steroids is the safest method of treatment. When immunoblastic sarcoma complicates immunoblastic lymphadenopathy combination chemotherapy is generally prescribed.

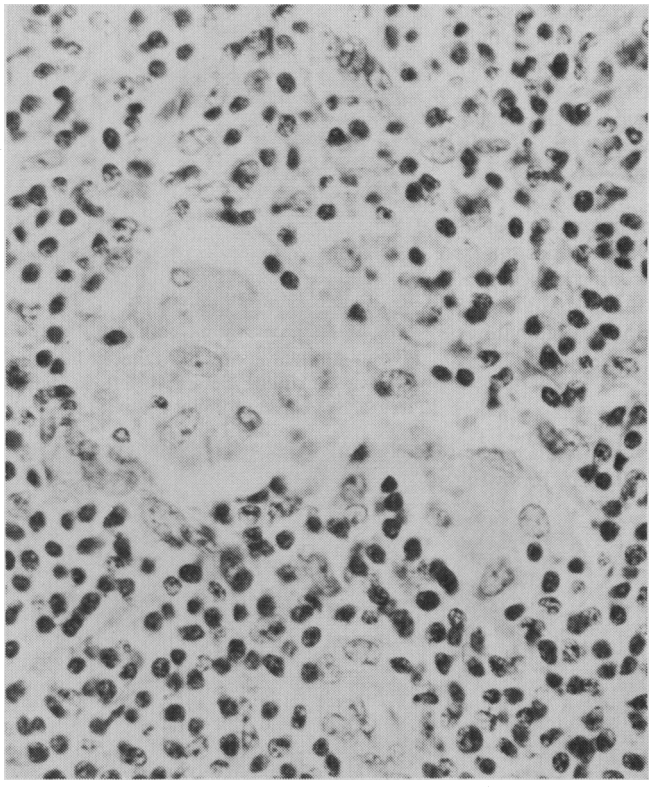

FIG. 1—Specimen of lymph node of patient 1, showing epithelioid granulomas surrounded by polymorphous cellular infiltrate (hematoxylin–eosin [H–E]; × 500).

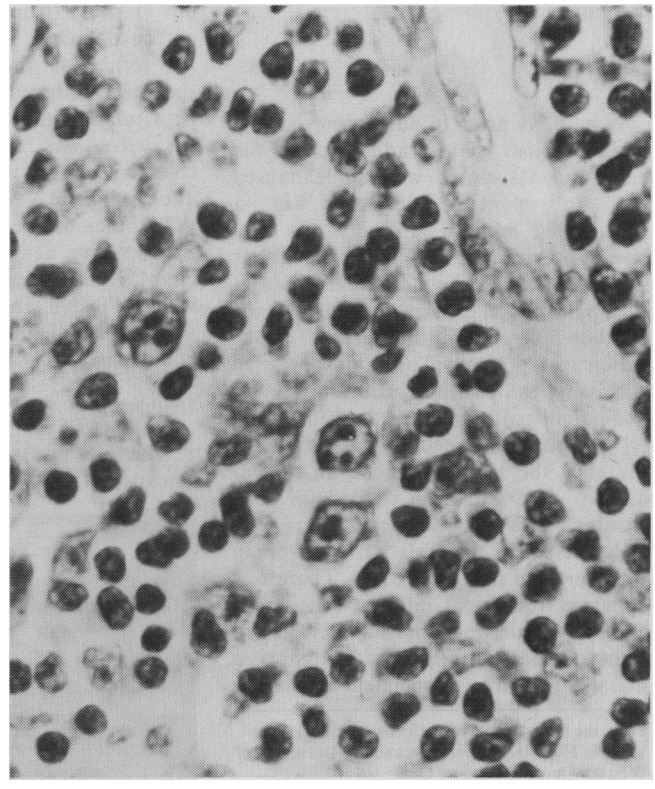

FIG. 2—Specimen of lymph node of patient 3, showing vascular proliferation, immunoblasts, lymphocytes and plasma cells (H–E; × 625).

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Intussusception in an adult: an unusual case

V.M. WALLEY, MD
D.P. GIRVAN, MD, M CL SC, FRCS[C]

Intussusception is a physiologically dynamic and clinically dramatic form of bowel obstruction. Although it occurs at all ages, there are important clinical and pathological differences between cases in adults, which are uncommon, and those in children, which are more frequent. These differences dictate distinct approaches to management. The following example of intussusception in an adult is not clinically atypical but is pathologically unusual.

Case report

Nine days prior to admission, colicky midabdominal pain radiating to the back and associated with some nausea but no vomiting developed in a 71-year-old woman. Initially she had some watery diarrhea without blood, but it lessened over the next several days. The pain and the diarrhea returned for another 5 days, and antidiarrheal medication was prescribed. The day prior to admission the patient had more crampy abdominal pain that increased in severity, but she continued to pass stool. In the past she had undergone an appendectomy and had been treated for pericarditis and congestive heart failure.

At the time of admission the woman was alert and in mild distress. There was apparent abdominal fullness, diffuse abdominal tenderness, particularly to the right of the umbilicus, and possibly a mass in this area, associated with minimal guarding. Rectal examination showed soft stool with occult blood. The hemoglobin level was 15.7 g/dl and the leukocyte count 8.7×10^9/l.

A clinical diagnosis of obstruction of the small bowel was confirmed by abdominal roentgenography. A barium enema revealed an intussusception just proximal to the hepatic flexure (Fig. 1), which was reduced to the cecum with the usual infusion pressure of the barium (Fig. 2). Complete reduction could not be obtained, and the barium would not reflux, so the intussusception was surgically reduced. At the same time, a firm tumour in the region of the ileocecal valve was removed with a right colectomy. The patient's recovery was uncomplicated.

Pathological examination of the surgical specimen demonstrated a circumferential villous adenoma of the ileocecal valve (Figs. 3 and 4), no malignancy, and five small tubular and tubulovillous adenomas.

Discussion

In adults intussusception is an unusual cause of bowel obstruction, following hernias, adhesions, volvulus and carcinomas in incidence.[1] In children, however, it is the commonest cause of bowel obstruction; 60% to 70% of affected

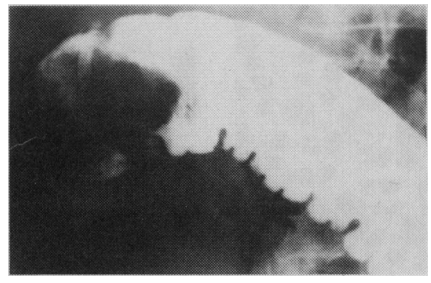

FIG. 1—Barium fills transverse colon to hepatic flexure, where it is obstructed by tumour mass.

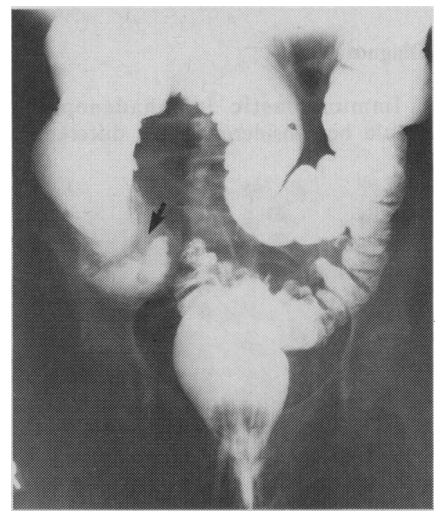

FIG. 2—Barium enema has reduced intussusception, but filling defect is left in cecum (arrow), and barium will not reflux.

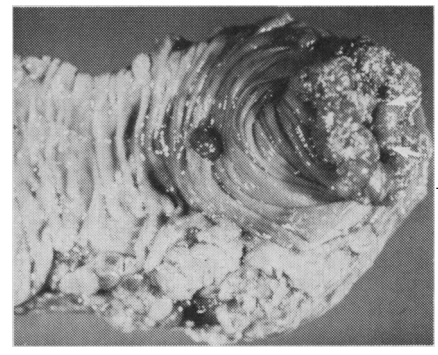

FIG. 3—Villous adenoma encircling lumen (arrows) of ileocecal valve, and small tubular adenoma to the left.

From the departments of pathology and surgery, Victoria Hospital Corporation and the University of Western Ontario, London, Ont.

Reprint requests to: Dr. V.M. Walley, Department of pathology, Victoria Hospital Corporation, 375 South St., London, Ont. N6A 4G5